Synthesis and insecticidal activity of novel 1,3,4-oxadiazolin-5-one and pyrazolin-5-one derivatives

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Abstract: A series of novel 2-(2,4,6-trisubstituted phenyl)-1,3,4-oxadiazolin-5-one derivatives and 3-(2,4,6-trichlorophenyl)pyrazolin-5-one derivatives were synthesized and evaluated for insecticidal activity. It was found that a moderately bulky alkyl group, such as a *tert*-butyl group, on the heterocyclic ring, and a trifluoromethyl group on the benzene ring were optimal substituents on the molecule. The oxygen atom in the oxadiazoline ring was essential for insecticidal activity. Of the compounds assayed, 4-tert-butyl-2-(2,6-dichloro-4-trifluoromethylphenyl)-1,3,4-oxadiazolin-5-one gave the highest activity against *Nephtotettix cincticeps*, with an LC_{50} value of 0.51 mg litre^{-1}.

Keywords: insecticidal activity; heterocycles; 2,4,6-trisubstituted benzene; structure–activity relationships

1 INTRODUCTION

It has been reported that nitrogen-containing heterocyclic compounds having a multi-substituted aryl group, such as the 2,4,6-trisubstituted phenyl group[1–6] or a 3,5-disubstituted 2-pyridyl group,[7] exhibit insecticidal activity. Of the heterocycles, fipronil (Fig 1; **A**),[3] an *N*-phenylpyrazole derivative, has recently been marketed as the first example of a practical insecticide of this class. Modes of action of the heterocycles have also been investigated and were found mainly to be novel GABA-gated chloride ion channel inhibitors,[1–3] or sodium channel blockers such as the triazole derivative **B**[4] (Fig 1).

It is of great interest to find whether other heterocycles which have not been reported in literature or patent literature could, in combination with the multi-substituted aryl group, provide novel classes of insecticide. In the majority of reported heterocyclic compounds the multi-substituted aryl group and the heterocyclic ring are linked through the carbon atom on the aryl ring and the nitrogen atom on the heterocyclic ring (C–N linkage). However, a few examples[5–7] can be found of the derivatives possessing a linkage between a carbon atom on the aryl ring and a carbon atom on the heterocyclic ring (C–C linkage), such that the compounds can be expressed as the general structure shown in Fig 2. Detailed biological profiles on these derivatives having a carbon–carbon bond between the rings have not been reported so far. Therefore, these kinds of C–C linked heterocycles are of great interest as possible novel biologically active compounds.

In the course of our study on C–C linked heterocycles, we have synthesized novel 2-(2,4,6-trisubstituted phenyl)-1,3,4-oxadiazolin-5-one derivatives, and their structural analogue, 3-(2,4,6-trichlorophenyl)pyrazolin-5-one. Evaluation of these

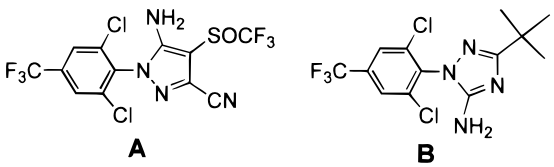

Figure 1. Structures of reported nitrogen-containing heterocyclic compounds having a 2,4,6-trisubstituted phenyl group.

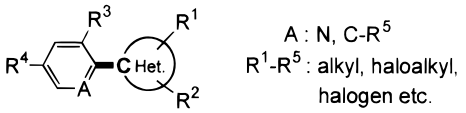

Figure 2. General structure of C–C linked heterocycles having a multi-substituted aryl group.

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derivatives against hemipteran, coleopteran and lepidopteran insects, and an acarina mite showed insecticidal activities, and particularly, strong activity against the green leafhopper, *Nephotettix cincticeps* (Uhl). Here, we report the synthesis of these novel classes of C–C linked heterocycles, the insecticidal activities of the compounds, and structure–activity relationships in these series.

2 METHODS

Melting points were measured with a Yanagimoto micromelting point apparatus and were uncorrected. Refractive Index was measured with an Atago 3T refractometer. [^{1}H]NMR (60 MHz) was recorded in deuterochloroform, using tetramethylsilane as an internal standard, with a Hitachi R-1200 or JEOL PMX-60 SI NMR Spectrometer. Electron-impact mass spectra were measured on JEOL JMS AM-50.

2.1 Synthesis

Synthetic methods for each type of compound are outlined in Figs 3 and 4 and typical examples are described below; the yields were not optimized.

2.1.1 1,3,4-Oxadiazolin-5-one derivatives

2-(2,4,6-Trisubstituted phenyl)-1,3,4-oxadiazolin-5-one and -5-thione derivatives were prepared as depicted in Fig 3.

4-*tert*-Butyl-2-(2,4,6-trisubstituted phenyl)-1,3,4-oxadiazolin-5-one derivatives, as in **1** and **7**, were synthesized by the reaction between *N*-*tert*-butyl-*N*'-2,4,6-trisubstituted benzoylhdrazines and trichloromethyl chloroformate, following the method reported in the patent literature.[8] *N*-*tert*-Butyl-*N*′-2,4,6-trisubstituted benzoylhydrazines were obtained from the corresponding 2,4,6-trisubstituted benzoyl chloride and *tert*-butylhdrazine hydrochloride. 4-*tert*-Butyl-2-(2,4,6-trichlorophenyl)-1,3,4-oxadiazoline-5-thione (**6**) was prepared from *N*-*tert*-butyl-*N*′-2,4,6-trichlorobenzoylhydrazine and thiophosgene. 4-Substituted 2-(2,4,6-trichlorophenyl)-1,3,4-oxadiazolin-5-one, other than 4-*tert*-butyl derivatives, as in **2**, **3** and **4**, were synthesized from 2-(2,4,6-trichlophenyl) -4*H*-1,3,4-oxadiazolin-5-one-and the corresponding alkyl iodide. 2-(2,4,6-Trichlorophenyl)-4*H*-1,3,4-oxadiazolin-5-one was prepared by the reaction between 2,4,6-trichlorobenzoylhydrazine and trichloromethyl chloroformate in the manner given above. A reaction between 5-mercapto-2-(2,4,6-trichlorophenyl)-1,3,4-oxadiazole, which was also derived from 2,4,6-trichlorobenzoylhydrazine, and dibromodifluoromethane gave two reaction products: 4-bromodifluoromethyl-2-(2,4,6-trichlorophenyl)-1,3,4-oxadiazoline-5-thione (**5**) and 5-bromodifluoromethylthio-2-(2,4,6-trichlorophenyl)-1,3,4-oxadiazole. These compounds were separated by silica gel column chromatography and identified by the analysis of the fragmentation pattern on electron-impact mass spectra.

2.1.1.1 4-tert-Butyl-2-(2,4,6-trichlorophenyl)-1,3,4-oxadiazolin-5-one (***1***).[8] A solution of trichloromethyl chloroformate (0.3 ml) in tetrahydrofuran(3 ml) was added to a mixture of *N*-*tert*-butyl-*N*′-2,4,6-trichlorbenzoylhydrazine (0.70 g; 2.4 mmol), pyridine (0.47 g; 6.0 mmol) and tetrahydrofuran (10 ml) under ice-water cooling. The mixture was stirred for 1.5 h at room temperature. Aqueous ammonia was added to the resulting mixture, which was then extracted with ethyl acetate. The organic layer was washed with water and dilute hydrochloric acid, and dried over sodium sulfate. Removal of the solvent gave 4-*tert*-butyl-2-(2,4,6-trichlorophenyl)-1,3,4-oxadiazolin-5-one (**1**) as a solid; 0.75 g (97%), mp 80.5–83.0°C; [^{1}H[-NMR (δ ppm); 1.60 (s, 9H), 7.45 (s, 2H); Mass (EI); 320 (M^+).

2.1.1.2 4-Bromodifluoromethyl-2-(2,4,6-trichlorophenyl)1,3,4-oxadiazoline-5-thione (***5***). A mixture of 2,4,6-trichlorobenzoylhydrazine (7.0 g; 29 mmol), potassium hydroxide (2.0 g; 30 mmol; as 850 g litre^{-1} aqueous solution), carbon disulfide (7 ml) and ethanol (50 ml) was refluxed overnight. After removal of the volatile materials, water and dilute hydrochloric acid were added to cause precipitation. Collection of the precipitates and washing with water gave 5-mercapto-2-(2,4,6-trichlorophenyl)-1,3,4-oxadiazole (7.0 g; 86%). To a stirred suspension of sodium hydride (0.37 g; 8.4 mmol; 55% in oil) and

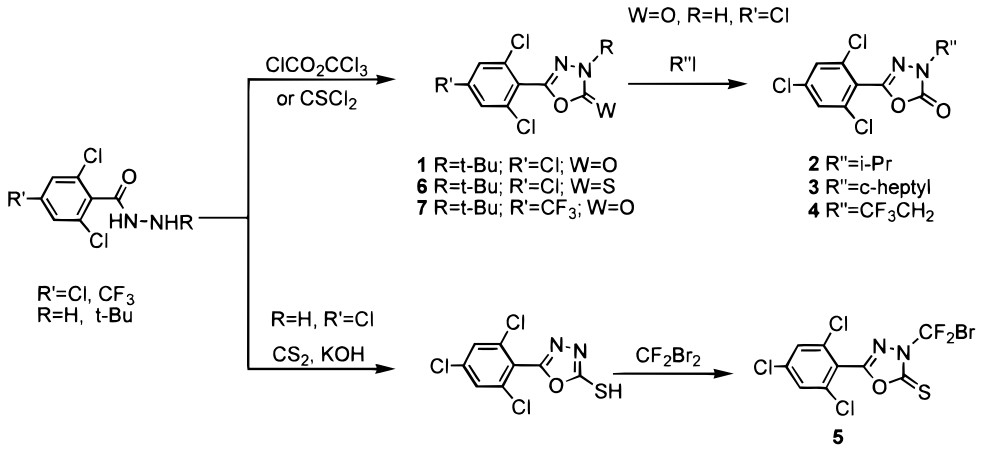

Figure 3. Synthetic pathway to 2-(2,4,6-trisubstitutedphenyl)-1,3,4-oxadiazolin-5-one and -5-thione derivatives.

dimethylformamide (DMF; 10 ml), a solution of the 5-mercapto-1,3,4-oxadiazoline (2.0 g; 7 mmol) in DMF (5 ml) was added under ice-water cooling. Stirring was continued for an additional 0.5 h at room temperature, dibromodifluoromethane (5.3 g; 25 mmol) then added, and the mixture was heated for 8 h at 100°C. The resulting mixture was poured onto ice-water, and extracted with ethyl acetate. The organic layer was washed with water and dried over sodium sulfate. Removal of the solvent gave an oily residue, which was subjected to preparative thin-layer chromatography, eluting with chloroform, to separate the desired oxadiazoline-5-thione and oxadiazole derivatives. 4-Bromodifluoromethyl-2-(2,4,6-trichlorophenyl)-1,3,4-oxadiazoline-5-thione (**5**): Yield; 0.58 g (20%); $n_D^{22.5} = 1.5330$ [^{1}H]NMR (δ, ppm); 7.56 (s, 2H); Mass (EI); 408 (M^+), 330(-Br), 269, 205. 5-Bromodifluoromethylthio-2-(2,4,6-trichlorophenyl)-1,3,4-oxadiazole: Yield: 0.72 g (25%); $n_D^{22.5} = 1.5422$; [^{1}H]-NMR (δ, ppm); 7.60 (s, 2H); Mass (EI); 408 (M^+), 330 (−Br), 269, 247 (−SCF_2Br), 219, 205.

2.1.2 Pyrazolin-5-one derivatives

1-*tert*-Butyl-3-(2,4,6-trichlorophenyl)pyrazolin-5-one (**8**) was synthesized from 2,4,6-trichlorobenzoyl chloride *via* ethyl 2-ethoxycarbonyl-3-hydroxy-3-(2,4,6-trichlorophenyl)acrylate and ethyl 3-hydroxy-3-(2,4,6-trichlorophenyl)acrylate[9] as shown in Fig. 4.

2.1.2.1 1-tert-Butyl-3(2,4,6-trichlorophenyl)pyrazolin-5-one (**8**). A mixture of ethyl 3-hydroxy-3-(2,4,6-trichlorophenyl)acrylate (3.0 g; (10 mmol), *tert*-butylhydrazine hydrochloride (1.25 g; 10 mmol), a catalytic amount of *p*-toluene sulfonic acid and toluene (30 ml) was refluxed under a Dean-Stark condenser for 20 h. Ethyl acetate was added to the resulting mixture which was washed with water, and dried over sodium sulfate. Removal of the solvent gave an oily residue, which was subjected to preparative thin-layer chromatography to obtain pure 1-*tert*-butyl-3-(2,4,6-trichlorophenyl)-pyrazolin-5-one (**8**) as a solid; 0.60 g (19%); mp 167–169.5°C; [^{1}H]-NMR (δ, ppm); 1.56 (s, 9H), 3.59 (s, 2H), 7.43 (s, 2H) Mass (EI); 318 (M^+).

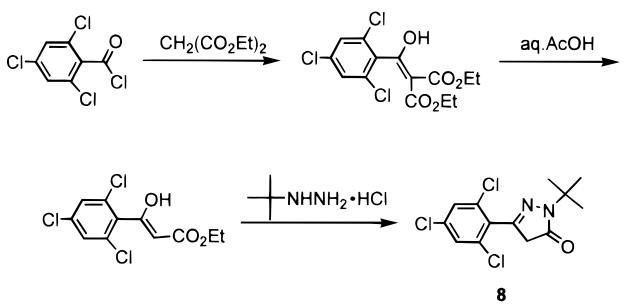

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Figure 4. Synthetic pathway to 1-*tert*-butyl-3-(2,4,6-trichlorophenyl)pyrazolin-5-one (**8**).

2.2 Biological assay

Biological assays were conducted against the green rice leafhopper, *Nephotettix cincticeps*, the brown planthopper, *Nilaparvata lugensstahl*, the 28-spotted lady beetle, *Epilachna vigintioctopunctata F*, the two-spotted spider mide (*Tetranychus urticae* Koch) and the diamond-back moth, *Plutella xylostella* (*L*).

Each test compound was formulated as an emulsifiable concentrate which was then diluted to six rates with water containing a surfactant. Commercially available imidacloprid 100 g kg^{-1} ('Admire') and buprofezin 250 g kg^{-1} ('Applaud') wettable powders were used as reference compounds.

2.2.1 Brown planthopper (Nilaparvata lugens) and the green rice leafhopper (Nephotettix cincticeps)

Rice stems were immersed in each solution for 20 s. Each treated stem was put into a glass tube (2 cm diameter × 10 cm height) with a small amount of water. After drying, seven third-instar nymphs of *N. lugens* or *N. cincticeps* were released into each tube, which was kept at 25°C, 70% RH under long-day (16L: 8D) conditions. Mortality was observed six days later. Thirty to forty larvae were used for each treatment with two replications.

2.2.2 Twenty-eight-spotted lady beetle (Epilachna vigintioctopunctata) and diamond back moth (Plutella xylostella)

Tomato leaf-cuts were immersed in solutions for 20 s. Each treated leaf cut was placed in a petri dish (3 cm diameter) and seven third-instar larvae of *E. vigintioctopunctata* were released in to each dish. Treated insects were kept at 25°C, 70% RH under long-day(16L : 8D) conditions. Mortality was observed six days later. Thirty to forty larvae were used for each treatment with two replications.

The same procedure was used for *P. xylostella* on cabbage leaf-cuts.

2.2.3 Two-spotted spider mite (Tetranychus urticae)

Newly hatched larvae of *T. urticae* on kidney bean leaf discs (prepared by the Rothamsted method) were sprayed with aqueous dilutions of the chemicals via a rotary spray tower giving a standard deposit of 2.5 mg cm^{-2}. Treated mites were kept at 25°C, 70% RH under long-day(16L : 8D) conditions. Mortality was observed six days later. Thirty to forty larvae were used for each treatment, with two replications.

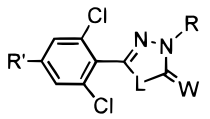
The LC_{50} values were estimated in each case by probit analysis.

RESULTS AND DISCUSSION

Table 1 gives results for a series of 1,3,4-oxadiozolin-5-one derivatives and their structural analogue pyrazolin-5-one derivative, in which substituents and part of the structure of the molecule were varied.

For the initial investigation regarding molecular design in this series, we examined the combination of

Table 1. Insecticidal activity of 2-(2,4,6-trisubstituted phenyl)-1,3,4-oxadiazolin-5-one derivatives and 1-*tert*-butyl-3-(2,4,6-trichlorophenyl)pyrazolin-5-one derivatives against *Nephotettix cincticeps*



Compound	R	R′	W	L	mp(°C) or $n_D^{22.5}$	LC_{50} (mg litre^{-1})
1	*tert*-Bu	Cl	O	O	80.5–83.0	23.1
2	iso-Pr	Cl	O	O	87.5–90.0	121.9
3	*cyclo*-heptyl	Cl	O	O	98.0–100.5	251.2
4	CH_2CF_3	Cl	O	O	81.0–82.0	>500
5	CF_2Br	Cl	S	O	1.5330	60.9
6	*tert*-Bu	Cl	S	O	87.0–89.5	72.8
7	*tert*-Bu	CF_3	O	O	26.0–27.0	0.51
8	*tert*-Bu	Cl	O	CH_2	167–169.5	>500

a *tert*-butyl group, as a substituent on the oxadiazoline ring and 2,4,6-trichlorobenzene as the aryl group. Thus, 4-*tert*-butyl-2-(2,4,6-trichlorphenyl)-1,3,4-oxadizolin-5-one (**1**) was designed and synthesized. As expected, it showed insecticidal activity against *N cincticeps* with an LC_{50} value of 23.1 mg litre^{-1}.

Structural variations were then made to optimize the insecticidal activity as well as to investigate structural requirements for exhibiting optimal activity in this class of compounds. One of the key moieties to exhibit optimal insecticidal activity is considered to be the alkyl group at the 4-positon on the oxadiazoline ring. Introduction of an isopropyl group (**2**) or a cycloheptyl group (**3**) at this position, as substituents less or more bulky than the *tert*-butyl group, reduced the activity, with LC_{50} values of 121.9 and 251.2 mg litre^{-1}, respectively. The results indicate that correct bulk of the substituent at the 4-position is required for activity, and the optimal volume would be the size of the *tert*-butyl group. In order to examine effects of the electronic properties of the substituent, haloalkyl groups such as a trifluoroethyl (**4**) and a bromodifluoromethyl group (**5**) were introduced. The trifluoroethyl group seemed not to be suitable at this position, as the insecticidal activity disappeared altogether, but the bromodifluoromethyl group maintained some activity, LC_{50} : 60.9 mg litre^{-1} In other parts of the molecule, replacement of the carbonyl group at the 5-position by a thiocarbonyl group (**6**) slightly reduced the insecticidal activity. The introduction of a trifluoromethyl group at the 4-position on the benzene ring (**7**) greatly improved the activity (LC_{50} : 0.51 mg litre^{-1}) which was the highest in this series. The action of compound **7** was rapid, with mortality within 1–2 h.

Replacement of the oxygen atom of compound **1** by CH_2, as in compound **8**, resulted in complete loss of activity. The result suggests that the oxygen atom in the ring at this position is necessary to provide the correct electronic configuration to express insecticidal activity. It may be postulated that this plays a role in the interaction of the compounds with a receptor as a ligand.

To investigate the insecticidal spectrum of the series of oxadiazolin-5-one derivatives, some other species, *N. lugens*, *T. urticae*, *E. vigintioctopunctata*, *P. xylostella*, were assayed. LC_{50} values for selected compounds, **1**, **6** and **7**, were compared with those for conventional insecticides, imidacloprid and buprofezin, which are currently used in paddy fields as agents against Hemipteran insects. The results, including *N cincticeps*, are shown in Table 2.

The compounds assayed exhibited activities against *E. vigintioctopunctata* and *P. xylostella* at levels of 250–320 and 590 mg litre^{-1}, respectively. However, they were inactive against *T. urticae*. As discussed, compound **7** showed strong activity against *N. cincticeps*, which was almost comparable to that of the conventional insecticides. Susceptibilities varied among Hemipteran species and compound **7** was inactive against *N. lugens*.

In summary, a series of novel 2-(2,4,6-trisubstituted phenyl)-1,3,4-oxadiazolin-5-one derivatives with a C–C linked to a 2,4,6-trisubstituted phenyl moiety have been shown to have insecticidal activity. Some structural requirements to confer the activity

Table 2. Evaluation of insecticidal spectrum on selected compounds

Compound	LC_{50} (mg litre^{-1})[a]				
	NL	NC	EV	PX	TU
1	>500	23.1	317.3	N[b]	>500
6	>500	72.8	>500	590.2	>500
7	>500	0.51	251.2	N	>500
Imidacloprid	0.05	0.3	N	175.2	>500
Buprofezin	0.3	0.3	N	N	N

a NL: *N. lugens*; NC: *N. cincticeps*; EV: *E. vigintioctopunctata*; TU: *T. urticae*; PX: *P. xylostella*.
b N: not tested.

were confirmed; a *tert*-butyl group, as a moderately bulky alkyl group on the heterocyclic ring and trifluoromethyl group on the benzene ring are optimal substituents in this series.

An oxygen atom as a heteroatom in the oxadiazoline ring was revealed to be essential for insecticidal activity. Among the species assayed, strong insecticidal activity was found against *N. cincticeps* by 4-*tert*-butyl-2-(2,6-dichloro-4-trifluoromethyl phenyl)-1,3,4-oxadiazolin-5-one, with an LC_{50} value of 0.51 mg litre^{-1}.

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